II. REMARKS

A. Status of Claims

Claims 1, 4, 6, 8-20, 24-33 and 35-39 are pending in this application. The claims are not being amended in this response.

B. 35 U.S.C. §103 Rejection over U.S. Patent No. 5,055,306 to Barry et al.

In the Office Action, claims 1, 4, 6, 8-20, 24-33 and 35-39 were rejected under 35 U.S.C. §103(a) as being unpatentable over Barry et al (US 5,055,306). The Office Action alleged that the "broad claim to sustained release metformin formulation reads on the disclosure of Barry" and that "the properties applicant discloses and/or claims are necessarily present. The Examiner further states that "[a]bsent a showing of factual evidence, the metformin formulation of Barry would have the properties and functions recited in the instant claims."

This rejection is traversed. In response to the Examiner's request, Applicants submit herewith "factual evidence" that one skilled in the art would expect that the formulation of Barry would not have the properties and functions recited in the instant claims (i.e., an increase in AUC (bioavailability) in the presence of food).

Applicants submit herewith as Exhibit A, a copy of U.S. Patent No. 4,900,558 ("the '558 patent) which has overlapping inventorship with the Barry reference and has the same assignee. As demonstrated in the following chart, the formulations of the '558 patent are substantially similar to the formulations of the Barry reference:

The Barry reference	' 558 Patent
Size of granules = 0.5-2.5 mm (See Abstract)	Size of granules = 0.5-2 mm (see Abstract)
Core = active + excipient (See Abtract) The active can be ibuprofen and microcrystalline cellulose (See, e.g., column 9, lines 15-20)	Core = ibuprofen (active) + microcrystalline cellulose (excipient)
Coating = 100 parts water insoluble, water swellable acrylic polymer + 20-70 parts hydroxylated cellulose derivative (See Abstract)	Coating = 100 parts water insoluble, water swellable acrylic polymer + 20-70 parts hydroxylated cellulose derivative (See Abstract)
Coating weight = 2-25% of core (See Abstract)	Coating weight = 5-20% of core (See Abstract)

Applicants note that the formulations of the Barry reference further contain an effervescent or water dispersible ingredient which is not included ~~the~~ the formulations of the '588 patent. However, Applicants respectfully submit that after the Barry formulations are placed in the patient's mouth, the effervescent or water dispersable ingredient causes the formulation to break apart and disperse into the virtually same formulation as described in the '558 patent. Therefore, the formulation of the Barry reference which is ultimately swallowed, is virtually identical to the formulations of the '558 patent.

Applicants respectfully submit that as the formulation of the Barry reference that is ultimately swallowed and the formulation of the '558 patent are virtually identical, the properties and functions of the formulations of the Barry reference and the '558 patent would also be virtually identical. On this note, Applicants direct the Examiner's attention to column 4, line 67-column 5, line 8 of the '558 patent, which recites:

> A further advantage of the present formulation is that it can be taken with or without food. **If the formulation is taken with food, the time taken to reach its peak plasma concentration in**

> **plasma is about the same as if it is taken without food, whereas the peak plasma concentration is slightly reduced and the absorption is spread over a slightly longer period**. However, these differences are only minor and can for practical purposes be ignored, as the usual statistical tests did not show them to be significant.
> '558 patent at column 4, line 67- column 5, line 8 (emphasis added).

As indicated above, the '558 patent describes a formulation which possesses properties which are not significantly affected by the presence of food. Therefore, Applicants submit that the formulations of the Barry reference would also possess properties which are not significantly effected by the presence of food. Accordingly, one of ordinary skill in the art would expect that the formulations of the Barry reference would not have the same properties and functions as the claimed formulation (i.e., an increase in AUC (bioavailability) in the presence of food) as the formulation of the Barry reference are not significantly affected by the presence of food.

Regardless of the argument presented above, Applicants respectfully submit that the Examiner has not met her burden of proof to establish that the claimed pharmacokinetic parameters (*i.e.*, providing therapeutic levels of metformin over a 24 hour period and providing an AUC which is increased by the presence of food) are necessarily present in the formulations described in Barry et al. However, assuming arguendo that the Examiner has met this burden, Applicants respectfully submit that the evidence presented above establishes that the formulations of the prior art would not be expected to provide the pharmacokinetic parameters recited in the present claims.

In view of the above, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

C. Rejection of method claims 33 and 35 over the Barry reference

In the Office Action, the Examiner stated that "[r]egarding claims 33 and 35, it is noted that the formulation of Barry is orally administered and the oral administration involves swallowing and because the drugs are the same and method step is oral administering, which involves swallowing, the metformin would provide the same effect as that which is claimed. Therefore, Barry discloses the method of claims 33 and 35."

Applicants respectfully submit that in making this statement, it appears that the Examiner has not considered all of the limitations of claims 33 and 35, which are presented below:

> 33. A method of treating a human diabetic patient with an oral solid dosage form of metformin, comprising: swallowing on a once a day basis in the presence of food an intact controlled release oral dosage form containing (i) an active agent consisting of an effective amount of metformin or a pharmaceutically acceptable salt thereof and one or more materials controlling the release of metformin from the dosage form such that therapeutic levels of said metformin are attained in said human for 12 to 24 hours and a decrease in the bioavailability of metformin is not exhibited.
>
> 35. A method of treating diabetes in humans, comprising:
> swallowing on a once a day basis in the presence of food an intact controlled release solid oral dosage form containing (i) an active agent consisting of a therapeutically effective metformin or a pharmaceutically acceptable salt thereof, and (ii) a sustained release material, such that therapeutic plasma levels of metformin are attained in said human over the dosing interval and (i) a decrease in the bioavailability of metformin is not exhibited relative to administration of the dosage form in the fasting state; or (ii) an increase in the bioavailability of metformin is exhibited relative to administration of the dosage form in the fasting state.
> (Emphasis added)

Applicants respectfully submit that the Barry reference does not teach or suggest swallowing an intact dosage form. Rather, the Barry reference teaches that the formulations described therein are disintegrated in an aqueous liquid prior to administration (See, e.g., col. 5, lines 43-55 of Barry) or by sucking and swallowing material released from the tablet (See, e.g.,

col. 10, lines 46-54 of Barry). Barry fails to teach or suggest a **method of treatment** comprising "...**swallowing** an **intact** dosage form..." as recited in independent claims 33 and 35 as the dosage forms of Barry are not swallowed intact, but rather, are taught to be swallowed non-intact (e.g., dispersed or effervesced).

In view of Barry, one of ordinary skill in the art would not be motivated to treat a human patient comprising swallowing an intact controlled release dosage form as recited in claims 33 and 35 of the present invention, as the tablets of the Barry reference are taught to be administered by dispersing or effervescing the formulations in the mouth of the patient, such that the formulations are swallowed non-intact (e.g., dispersed or effervesced).

In view of the above, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

C. Conclusion

It is respectfully submitted that in view of the arguments presented, that this case is now in condition for allowance. An early and favorable action on the merits is earnestly solicited.

According to currently recommended Patent Office policy the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
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